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(71) Applicant (*for all designated States except US*): SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventor; and

(75) Inventor/Applicant (*for US only*): ROYSTON, Maureen, Claire [GB/GB]; Charing Cross and Westminster Medical School, St. Dunstans Road, London W6 8RP (GB).

(74) Agent: FLORENCE, Julia; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

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(54) Title: METHOD OF PREDICTING A SUBJECTS RESPONSE TO NEUROLEPTIC AGENTS

(57) Abstract

A method of assessing in a subject the likelihood whether said subject will be non-responsive or responsive to treatment with a drug the primary mode of action of which is via a process of altered synaptic activity, the method comprising detecting the presence or absence of DNA comprising the E2 allele of the ApoE gene, or of protein expressed by said DNA, in a biological sample obtained from said subject. The method is exemplified with an atypical neuroleptic agent, i.e. clozapine.

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METHOD OF PREDICTING A SUBJECTS RESPONSE TO NEUROLEPTIC AGENTS

The present invention relates to methods of assessing the responsiveness of individuals to neuroleptic agents such as clozapine.

Schizophrenia is a devastating psychiatric disease for which there is currently no cure, although advances are now being made in understanding its causes and controlling its symptoms. In general the age of onset is in late adolescence and it is a lifelong illness with a poor prognosis. Subjects suffering from schizophrenia may exhibit positive symptoms, for example delusions and hallucinations, and /or negative symptoms such as withdrawal, isolation and demotivation leading ultimately to social decline and withdrawl. There are 600,000 schizophrenics at any one time in the UK and their care has been reported to cost approximately 1.6% of the total healthcare budget. Therefore better targetting of effective drug treatments has the potential for considerable economic savings (British Journal of Psychiatry, (1994) **165** (suppl.25), 18-21).

Since the 1950's antipsychotic drugs (neuroleptics) have been available and are used with varying degrees of success to treat the positive symptoms of schizophrenia. However, the majority of these agents ("typical" neuroleptics) have little effect on the negative symptoms and furthermore have a number of side effects, the most distressing of which are movement disorders known as extrapyramidal side effects (eps). Examples of typical neuroleptics include haloperidol and sulpiride. Over 90% of patients in the UK are treated with such traditional antipsychotics but some 30% of patients fail to respond. The therapeutic effect of typical antipsychotic agents is believed to be exerted principally via blockade of dopamine D_2 receptors; however this mechanism is also thought to be responsible for the extrapyramidal side effects.

More recently second generation antipsychotic agents, so-called "atypical" neuroleptics, having enhanced efficacy and fewer side effects have been developed. These compounds appear to have a lower affinity for D_2 receptors than do the typical neuroleptics but they also interact with other receptors, notably the serotonin 5-HT_{2A} receptor and the dopamine D_4 receptor. Atypical neuroleptics provide advantages in that they improve both the positive and negative symptoms of schizophrenia and cause virtually no eps. An example of this type of drug is clozapine. However its use has been severely limited by controversy over its propensity to produce neutropenia and its expense; hence it is reserved for the treatment of schizophrenia in subjects who do not respond to other neuroleptics. However, within this patient group there remains a proportion of patients who are resistant to treatment even with clozapine. A test, therefore, that helps to predict those patients most likely to benefit from treatment with clozapine would be a valuable clinical decision making tool.

Further examples of "atypical" neuroleptics include risperidone, olanzapine, seroquel, sertindole and ziprasidone; all are antagonists at both dopamine D_2 and 5-HT_{2A} receptors.

Once schizophrenia has been diagnosed it is clearly desirable to select and administer the most appropriate therapy as quickly as possible. At present treatment with neuroleptics is largely a matter of trial and error, as there is no way of determining in advance whether a patient is likely to be responsive to a given drug treatment. Hence a patient may undergo several courses of treatment with various antipsychotic agents before non-responsiveness is established. In view of the side effects of these drugs it would be highly beneficial to avoid giving them to patients who may never respond; this is particularly important in the case of clozapine, in view of its known toxicity profile. Furthermore, it is generally found that the long-term outcome of the disease is improved if a patient is given the most effective drug therapy at the outset, rather than after one or more inappropriate drugs. Therefore a means of targetting those patients more likely to respond to drug therapy would be advantageous.

Recently, particular alleles of the apolipoprotein E (ApoE) gene have been shown to be associated with an increased risk of developing Alzheimer's disease (Corder et al; Science. 1993; 261 : 921). However, it has also been suggested that possession of an E2 allele of this gene may have a protective effect and reduce the likelihood of developing late-onset Alzheimer's disease. (Corder et al, Nature Genetics 1994; 7 : 180 - 183).

Our studies have shown no effect of ApoE genotype on the risk of developing schizophrenia. However, we have surprisingly found that in a population of diagnosed schizophrenic patients treated with clozapine, patients who possess an ApoE E2 allele are significantly less likely to respond to treatment with clozapine (hereinafter "non-responders") than patients who do not possess the E2 allele. Thus there is an apparent association between the presence of the E2 allele of the ApoE gene and failure to respond to treatment with clozapine. Presence of the E2 allele can therefore be utilised to predict which patients are least likely to respond to treatment with clozapine.

In practice, as indicated above, the use of clozapine and other atypical neuroleptic agents to treat schizophrenia is reserved for those individuals who have failed to respond to treatment with other neuroleptic agents, such as haloperidol. Thus the method may be used more generally to predict whether a patient is likely to respond to any of the existing typical or atypical neuroleptic agents.

The present invention therefore provides an objective method of assessing in a subject the likelihood whether said subject will be non-responsive or responsive to treatment with neuroleptics such as clozapine, the method comprising detecting the presence or absence of DNA comprising the E2 allele of the ApoE gene , or the protein expressed by said DNA, in said subject.

It will of course be understood by practitioners skilled in the treatment of schizophrenia that the method of the present invention does not give a precise or absolute identification of responders and non-responders but rather indicates a probability or likelihood of responsiveness and so can be used to aid and guide the clinical judgment of the physician. Thus, a subject found to possess the E2 allele will not necessarily be excluded from drug therapy; however such a finding may have the benefit that the patient is not subjected to prolonged treatment with an ineffective drug, once it is clear that no clinical response is forthcoming.

Those skilled in the treatment of schizophrenia will also appreciate that the terms "responders" and "non-responders" as used herein are terms well known in the art. In the clinic the degree of responsiveness to a neuroleptic agent such as clozapine is generally assessed according to well-established rating scales, such as the Global Assessment Scale (GAS) or the Brief Psychiatric Rating Scale (BPRS).

In a further embodiment the present invention provides a method for use in assessing whether a subject suffering from a condition which may be treated with a neuroleptic agent will be responsive to treatment with said neuroleptic agent, said method comprising the steps of:

(i) testing for the presence or absence of DNA comprising the E2 allele of the ApoE gene or the protein expressed by said gene in a sample containing DNA or protein obtained from said subject, and

(ii) comparing the result with a pre-determined correlation between the presence or absence of the ApoE E2 allele and the response to said neuroleptic agent obtained for a population of subjects suffering from said condition.

The pre-determined correlation utilised in step (ii) may itself be obtained by the following series of steps:

selecting a population or cohort of subjects diagnosed as suffering from a specified condition suitable for treatment with a neuroleptic agent;

treating said cohort with a specified neuroleptic agent;

monitoring the outcome of said treatment and identifying responders and non-responders to the said treatment,

taking from said cohort biological samples containing DNA or protein and testing this for the presence or absence of the ApoE E2 allele;

analysing the presence or absence of the ApoE E2 allele as between responders and non-responders;

making a comparison with the distribution of the ApoE E2 alleles in a control group of subjects, not suffering from said condition;

performing a statistical analysis to determine if there is a statistically significant association between presence or absence of the ApoE E2 allele and response to treatment.

The invention thus also provides a method for assessing whether a subject suffering from a condition which may be treated with a neuroleptic agent will be responsive to treatment with a specified neuroleptic agent, said method comprising the steps of:

(i) correlating the presence or absence of the ApoE E2 allele in a population of subjects suffering from a specified condition requiring treament with a neuroleptic agent with observed clinical response to said neuroleptic agent;

(ii) testing for the presence or absence of DNA comprising the E2 allele of the ApoE gene or the protein expressed by said gene in a sample containing DNA or protein obtained from said subject, and

(iii) comparing the result with the correlation between the presence or absence of the ApoE E2 allele and the response to said neuroleptic agent obtained for a population of subjects suffering from said condition.

In a yet further aspect the invention provides a method for generating a model to assess whether a subject is likely to be responsive to treatment with a neuroleptic agent which method comprises:

(i) treating a cohort of patients diagnosed as suffering from a specified condition (eg schizophrenia) which may be treated with a neuroleptic agent (eg clozapine) with said neuroleptic agent;

(ii) assessing the outcome of treatment so as to define responders and non-responders according to pre-determined criteria;

(iii) obtaining DNA or protein samples from the cohort of patients in (i);

(iv) obtaining DNA or protein samples from a control group of subjects diagnosed as not suffering from said condition;

(v) analysing the samples obtained in (iii) and (iv) to identify whether they possess the E2 allele of the ApoE gene;

(vi) calculating the distribution of the E2 allele in the samples from (iii) for responders and non-responders;

(vii) calculating the distribution of the E2 allele in the samples from (iv);

(viii) comparing the distributions obtained in (vi) and (vii);

(ix) comparing the distribution obtained in (vi) as between responders and non-responders

(x) performing statistical analysis on the results from (viii) and (ix) to generate a model for asssessing the probability of response to treatment with said neuroleptic agent, based on whether a subject possesses the E2 allele of the ApoE group.

The invention also provides a method for assessing whether a subject suffering from a condition which may be treated with a neuroleptic agent will be responsive to treatment with a specified neuroleptic agent, which comprises comparing said subject's genotype with the model described above.

It will be appreciated that in any of the above methods, one or more of the steps may be effected by a computer-contolled system. Thus, for example, once the biological samples have been obtained, genotyping may be carried out by a computer-controlled robotic system. A computer-controlled system may also be configured to make the comparison between the subject to be assessed and a pre-determined correlation or model. A computer controlled system may also be configured to give either a positive or negative readout depending on the outcome of the comparison. The present invention therefore extends to such computer-controlled or computer-implemented methods.

The steps of testing for and detecting the presence or absence of DNA encoding the ApoE E2 allele or the protein expressed by said gene may be carried out either directly or indirectly by any suitable means, such as by techniques well known in the art, and is preferably carried out *ex vivo* All generally involve the step of collecting a sample of biological material containing DNA or protein from the subject, and then detecting which alleles or protein the subject possesses from that sample. For example, the detecting step may be carried out by collecting a biological sample containing DNA from the subject, and then determining the presence or absence of DNA comprising the E2 allele in the biological sample. Any biological sample which contains the DNA or protein of that subject may be employed, including tissue samples and blood samples, with blood cells being a particularly convenient source. Determining the presence or absence of DNA comprising the E2 allele may be carried out with an oligonucleotide probe labelled with a suitable detectable group; by means of an amplification reaction such as a polymerase chain reaction or ligase chain reaction (the product of which amplification reaction may then be detected with a labelled oligonucleotide probe) or by means of restriction nuclease digestion and electrophoretic separation to detect restriction fragment length polymorphism (RLFP). Numerous different oligonucleotide probe assay formats are known which may be employed to carry out the present invention. Detection of the expressed protein may be effected by standard methods well known in the art.

The present invention has utility in enabling improvements in the clinical management of patients suffering from schizophrenia. By identifying in advance of treatment those who are not likely to respond to neuroleptics such as clozapine, it will be possible to avoid unnecessary and non-beneficial administration of such drugs together with the associated side effects and costs and instead to select a more appropriate form of therapy. Thus the invention provides direct benefits to the patient in terms of indicating the most appropriate therapy as early as possible in the treatment process and is of wider benefit in terms of health economics.

In addition the invention has utility in enabling effective and efficient design of clinical trials with neuroleptic agents. Thus in comparative trials with two or more neuroleptics, patients who are not likely to respond to either or any of the agents can be excluded.

The basis of the present invention, namely that patients possessing an E2 allele of the ApoE gene are less likely to respond to clozapine, is particularly surprising in view of the previous findings that possession of an E2 allele is associated with good prognosis in neurodegenerative conditions: a protective effect for the development of late onset AD (Corder et al., 1994), increased longevity, slower rate of decline in both AD (Petersen et al., 1995) and of dementia in Down's syndrome (Royston et al., 1994), reduced pathology following head injury (Nicoll et al 1995), improved recovery following coma (Sorbi et al 1995) and better response following treatment with cholinesterase inhibitors (Tacrine) and cholinergic agonists (Xanomaline).

Without wishing to be bound by theory, it is postulated that possession of an E2 allele confers on the synaptic system an enhanced ability to respond by resprouting and reconnection. This is beneficial in conditions such as AD, where synaptic connectivity is compromised. In contrast, the treatment of schizophrenia with neuroleptic drugs depends on their ability to block receptors and experimental studies indicate that an effect of such receptor blockade is enhanced synaptic density (resprouting). In general this mechanism of synaptic repair is not sufficient to overcome the theraputic effects of blockade. However, individuals who respond better or more efficiently to synaptic damage/blockade (carrying an E2 allele) may be able to overcome the blockade and would be expected to show a reduced clinical response to that blockade i.e. will be neuroleptic non-responders. Presence of an E2 allele may therefore be an important prognostic indicator of a patient's response to any drug whose primary mode of action is via a process of altered synaptic activity e.g. anti-epileptic or antidepressant drugs.

Thus in a further aspect, the present invention provides a method for assessing in a subject the likelihood whether said subject will be non-responsive or responsive to treatment with a drug whose primary mode of action is via a process of altered synaptic activity, the method comprising testing for an detecting the presence or absence of DNA comprising the E2 allele of the ApoE gene, or the protein expressed by said DNA.

The present invention may also be utilised in screening for drugs whose primary mode of action is via a process of altered synaptic activity, eg antipsychotic, anti-epileptic or antidepressant agents. Such screening may be useful to identify therapeutic agents which may be potentially useful in patients who are not responsive to existing drugs. Screening may be effected using in vitro methods or in vivo methods eg utilising transgenic animals, eg mammals such as mice, which express the E2 allelic variant of the ApoE gene. Such transgenic animals may be obtained using procedures which are standard in the field of genetic engineering.

EXAMPLE

METHODS

Clinical Data

All the patients (177) in this study were Western European Caucasians with a DSM-IIIR diagnosis of schizophrenia. The patients had shown prior resistance to two classes of neuroleptic medication equivalent to a dose of at least 1000mg chlorpromazine given for a period of at least six weeks. Clozapine was given at varying doses (125-600mg per day) according to clinical response and all patients were stable for at least three months before inclusion in this study. The Global Assessment Scale (GAS) (Endicott et al., 1976) was used to subdivide patients into two groups (responder:non-responder) with a cut-off criteria of an improvement in GAS of at least 20 points. All GAS scores were performed blind to the genetic data by a senior psychiatrist. A total of 115 patients were classified as responders and 58 as non-responders, data was unavailable on 4 patients.

Genotyping was carried out independently using blood samples obtained from the patients and employing standard methodology.

The correlated results are shown in Table 1 below

		ALLELE		TOTAL
		E2	NO E2	
CLINICAL	RESPONDERS	15	100	115(66.5%)
	NON-RESPONDERS	15	43	58 (33.5%)
RESPONSE	TOTAL	30 (17.3%)	143 (82.7%)	173

Pearson Co-efficient 4.42; degree freedom 1; significance p=0.035.

Claims:

1. A method of assessing in a subject the likelihood whether said subject will be non-responsive or responsive to treatment with a drug the primary mode of action of which is via a process of altered synaptic activity, the method comprising detecting the presence or absence of DNA comprising the E2 allele of the ApoE gene, or of protein expressed by said DNA, in a biological sample obtained from said subject.

2. A method for assessing whether a subject suffering from a condition which may be treated with a drug the primary mode of action of which is via a process of altered synaptic activity will be responsive to treatment with said drug, said method comprising the steps of:

(i) testing for the presence or absence of DNA encoding the E2 allele of the ApoE gene in a sample apt to contain DNA or protein obtained from said subject, and

(ii) comparing the result with the correlation between the presence or absence of the ApoE E2 allele and the response to said drug obtained for a population of subjects suffering from said condition.

3. A method according to claim 1 or claim 2, said method comprising the steps of:

(i) correlating the presence or absence of the ApoE E2 allele in a population of subjects suffering from a specified condition which may be treated with a drug whose primary mode of action is via a process of altered synaptic activity with observed clinical response to said drug;

(ii) testing for the presence or absence of DNA comprising E2 allele of the ApoE gene or the protein expressed by said gene in a sample containing DNA or protein obtained from said subject, and

(iii) comparing the result with the correlation between the presence or absence of the ApoE E2 allele and the response to said drug obtained in step (i) for a population of subjects suffering from said condition.

4. A method for generating a model to assess whether a subject is likely to be responsive to treatment with a specified drug whose primary mode of action is via altered synaptic activity which method comprises:

(i) treating a cohort of patients diagnosed as suffering from a specified condition which may be treated with such a drug with said specified drug;

(ii) assessing the outcome of treatment so as to define responders and non-responders according to pre-determined criteria;

(iii) obtaining DNA or protein samples from the cohort of patients in (i);

(iv) obtaining DNA or protein samples from a control group of subjects diagnosed as not suffering from said condition;
(v) analysing the samples obtained in (iii) and (iv) to identify whether they encode or comprise the E2 allele of the ApoE gene;
(vi) calculating the distribution of the E2 allele in the samples from (iii) for responders and non-responders;
(vii) calculating the distribution of the E2 allele in the samples from (iv);
(viii) comparing the distributions obtained in (vi) and (vii);
(ix) comparing the distribution obtained in (vi) as between responders and non-responders;
(x) performing statistical analysis on the results from (viii) and (ix) to generate a model for asssessing the probability of response to treatment with said specified drug, based on whether a subject possesses E2 allele of the ApoE gene.

5. A method for assessing whether a subject suffering from a condition which may be treated with a drug whose primary mode of action is via altered synaptic activity will be responsive to treatment with a specified such drug, which comprises comparing said subject's genotype with a model as claimed in claim 4.

6. A method according to any of claims 1 to 5 wherein at least one step is effected by a computer controlled system.

7. A method according to any of claims 1 to 6 wherein detection of the E2 allele of the ApoE gene is indicative of reduced response to treatment with said drug.

8. A method according to any of claims 1 to 7 wherein the drug is a neuroleptic agent.

9. A method according to any of claims 1 to 8 wherein the neuroleptic agent is atypical.

10. A method according to any of claims 1 to 9 wherein the neuroleptic agent is clozapine.

11. A method according to any of claims 1 to 9 wherein the neuroleptic agent is selected from risperidone, olanzapine, seroquel, sertindole and ziprasidone.

12. A method according to any of claims 1 to 7 wherein the drug is an anti-epileptic drug.

13. A method according to any of claims 1 to 7 wherein the drug is an anti-depressant drug.

14. Use of a transgenic animal which expresses the human ApoE gene containing the E2 allele to screen drugs whose primary mode of action is via a process of altered synaptic activity.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K, C12N, C07K, A01K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9529257 A2 (MARTINEX R & DINC.), 2 November 1995 (02.11.95), page 4, line 9 - line 20, see claims --	1-8,12-14
P,A	Dialog Information Service, file 154, Medline, Dialog accession no. 08723289, Medline accession no. 96379828, Harrington CR et al: "Apolipoprotein E type epsilon 4 allele frequency is increased in patients with schizophrenia", Neurosci Lett (IRELAND) Dec 29 1995, 202 (1-2) p101-4 --	1-14
A	WO 9525793 A1 (RHÔNEPOULENC RORER S.A.), 28 Sept 1995 (28.09.95) -- --------	14

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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Information on patent family members

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